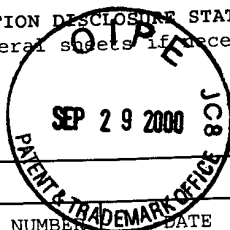


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U.S. PATENT DOCUMENTS

UNITED STATES PATENT & TRADEMARK OFFICE							
*EXAMINER INITIAL		DOCUMENT NUMBER	DATE	NAME	CLASS	SUBCLASS	FILING DATE
RRS	P1	5,141,957	Aug. 25, 1992	Jiang et al.	514	510	Nov. 5, 1990
RRS	P2	5,216,014	Jun. 1, 1993	Jiang et al.	514	455	Sep. 10, 1991
RRS	P3	5,270,310	Dec. 14, 1993	Bell et al.	514	238.2	Dec. 13, 1991
RRS	P4	5,292,737	Mar. 8, 1994	Defauw	514	247	Oct. 23, 1992
RRS	P5	5,344,841	Sep. 6, 1994	Jiang et al.	514	459	Jun. 8, 1992
RRS	P6	5,360,818	Nov. 1, 1994	Jiang et al.	514	459	Aug. 24, 1993
RRS	P7	5,432,198	Jul. 11, 1995	Jagdmann, Jr.	514	544	Aug. 18, 1994
RRS	P8	5,464,764	Nov. 7, 1995	Capecchi et al.	435	172.3	Feb. 4, 1993
RRS	P9	5,783,405	Jul. 21, 1998	Mochly-Rosen et al.	435	15	Oct. 10, 1995

FOREIGN PATENT DOCUMENTS

	DOCUMENT NUMBER	DATE	COUNTRY	CLASS	SUBCLASS	TRANSLATION	
						YES	NO
RRS	F1/ WO 98/17299	Apr. 30, 1998	WO	A61K	38/00		

OTHER PUBLICATIONS (including Author, Title, Date, Pertinent Pages, Etc.)

RRS	D1	✓	Allan et al, "Acute and Chronic Ethanol Treatments Alter GABA Receptor-Operated Chloride Channels," <u>Pharmacology Biochemistry and Behavior</u> , 27:665-670, (1987)
RRS	D2	✓	Berra et al, "Protein Kinase C $\zeta$ Isoform Is Critical for Mitogenic Signal Transduction," <u>Cell</u> , 74:555-563, (1993)
RRS	D3	✓	Chakravarthy et al, "The Direct Measurement of Protein Kinase C (PKC) Activity in Isolated Membranes Using a Selective Peptide Substrate," <u>Analytical Biochemistry</u> , 196:144-150, (1991)
	D4	✓	Chakravarthy et al, "Inactive membrane protein kinase Cs: a possible target for receptor signalling," <u>Biochem. J.</u> , 304:809-816, (1994)
RRS	D5	✓	Cooper et al, "Antagonism of the Enhanced Susceptibility to Audiogenic Seizures during Alcohol Withdrawal in the Rat by $\gamma$ -Aminobutyric Acid (GABA) and 'GABA-mimetic' Agents," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 209:396-403, (1979)
RRS	D6	✓	Crabbe et al, "Acute Dependence on Depressant Drugs is Determined by Common Genes in Mice," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 257(2):663-667, (1991)
RRS	D7	✓	Crabbe et al, "Elevated alcohol consumption in null mutant mice lacking 5-HT <sub>1B</sub> serotonin receptors," <u>Nature Genetics</u> , 14:98-101, (1996)
RRS	D8	✓	Crabbe et al, "Genetic Animal Models of Alcohol and Drug Abuse," <u>Science</u> , 264(5166):1715-1723, (1994)
RRS	D9	✓	Decock et al, "Classical, novel and atypical isoforms of PKC stimulate ANF- and TRE/AP-1-regulated-promoter activity in ventricular cardiomyocytes," <u>FEBS Letters</u> , 356:275-278, (1994)
RRS	D10	✓	Demarest et al, "Identification of an Acute Ethanol Response Quantitative Trait Locus on Mouse Chromosome 2," <u>The Journal of Neuroscience</u> , 19(2):549-561, (1999)

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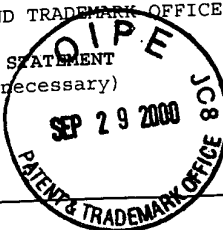
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RRS	D11	✓	Dewey et al, "A Novel Strategy for the Treatment of Cocaine Addiction," <u>Synapse</u> , 80:119-129, (1998)
RRS	D12	✓	Di Chiara et al, "Drugs abused by humans preferentially increase synaptic dopamine concentration in the mesolimbic system of freely moving rats," <u>Proc. Natl. Acad. Sci. USA</u> , 85:5274-5278, (1988)
RRS	D13	✓	Donzanti et al, "An improved and rapid HPLC-EC method for the isocratic separation of amino acid neurotransmitters from brain tissue and microdialysis perfusates," <u>Life Sciences</u> , 43:913-922, (1988)
RRS	D14	✓	Evans et al, "Establishment in culture of pluripotential cells from mouse embryos," <u>Nature</u> , 292:154-156, (1981)
RRS	D15	✓	Finn et al, "Temperature Dependence of Ethanol Depression in Mice: Dose Response," <u>Alcoholism: Clinical and Experimental Research</u> , 18(2):382-386, (1994)
RRS	D16	✓	Frye et al, "An Evaluation of the Locomotor Stimulating Action of Ethanol in Rats and Mice," <u>Psychopharmacology</u> , 75:372-379, (1981)
	D17	✓	Frye et al, "Differential Sensitivity of Ethanol Withdrawal Signs in the Rat to $\gamma$ -Aminobutyric Acid (GABA) Mimetics: Blockade of Audiogenic Seizures But Not Forelimb Tremors," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 226:720-725, (1983)
RRS	D18	✓	Gamache et al, "Simultaneous measurement of monoamines, metabolites and amino acids in brain tissue and microdialysis perfusates," <u>Journal of Chromatography</u> , 614:213-220, (1993)
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RRS	D20	✓	Goodnight et al, "Selective involvement of protein kinase C isozymes in differentiation and neoplastic transformation," <u>Advances in Cancer Research</u> , 64:159-209, (1994)
RRS	D21	✓	Gruber et al, "Increased Expression of Protein Kinase C $\alpha$ Plays a Key Role in Retinoic Acid-induced Melanoma Differentiation," <u>The Journal of Biological Chemistry</u> , 267(19):13356-13360, (1992)
RRS	D22	✓	Guidotti et al, "Gabaergic Synapses: Supramolecular Organization and Biochemical Regulation," <u>Neuropharmacology</u> , 22(12B):1471-1479, (1983)
RRS	D23	✓	Harris et al, "Functional Coupling of $\gamma$ -Aminobutyric Acid Receptors to Chloride Channels in Brain Membranes," <u>Science</u> , 228:1108-1110, (1985)
RRS	D24	✓	Hauger et al, "Corticotropin-Releasing Factor Receptors and Pituitary Adrenal Responses during Immobilization Stress," <u>Endocrinology</u> , 123:396-405, (1988)
RRS	D25	✓	Hesselbrock, "The Genetic Epidemiology of Alcoholism," in <u>The Genetics of Alcoholism</u> , 17-39, (Begleiter et al., eds., Oxford University Press, 1995)
RRS	D26	✓	Hodge et al, "Effects of Intraaccumbens Injections of Dopamine Agonists and Antagonists on Sucrose and Sucrose-Ethanol Reinforced Responding," <u>Pharmacology Biochemistry and Behavior</u> , 48(1):141-150, (1994)
RRS	D27	✓	Hodge et al, "Increased exploratory behavior and diminished anxiety in mutant mice lacking PKC $\epsilon$ ," <u>Society for Neuroscience Abstracts</u> , 24(1-2):117, (November 1998)
RRS	D28	✓	Homanics et al, "Alcohol and anesthetic mechanisms in genetically engineered mice," <u>Frontiers in Bioscience</u> , 3:548-558, (1998)

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D29	Hundle et al, "Overexpression of $\epsilon$ -Protein Kinase C Enhances Nerve Growth Factor-induced Phosphorylation of Mitogen-activated Protein Kinases and Neurite Outgrowth," <u>The Journal of Biological Chemistry</u> , 270(50):30134-30140, (1995)
D30	Hundle et al, "An Inhibitory Fragment Derived from Protein Kinase C $\epsilon$ Prevents Enhancement of Nerve Growth Factor Responses by Ethanol and Phorbol Esters," <u>The Journal of Biological Chemistry</u> , 272(23):15028-15035, (1997)
D31	Johannes et al, "PKC $\mu$ Is a Novel, Atypical Member of the Protein Kinase C Family," <u>The Journal of Biological Chemistry</u> , 269(8):6140-6148, (1994)
D32	Jolly et al, "In vivo microdialysis in the rat: low cost and low labor construction of a small diameter, removable, concentric-style microdialysis probe system," <u>Journal of Neuroscience Methods</u> , 68:259-267, (1996)
D33	Kellenberger et al, "Function of the $\alpha 1\beta 2\gamma 2\delta$ -Aminobutyric Acid Type A Receptor Is Modulated by Protein Kinase C via Multiple Phosphorylation Sites," <u>The Journal of Biological Chemistry</u> , 267(36):25660-25663, (1992)
D34	Kelley et al, "Absence of PKC $\epsilon$ produces changes in ethanol and GABA $_A$ agonist-induced sedation in mice," <u>Society for Neuroscience Abstracts</u> , 24(1-2):2166, (November 1998)
D35	Kitano et al, "Assay and Purification of Protein Kinase C," <u>Methods in Enzymology</u> , 124:349-352, (1986)
D36	Koob et al, "Neuroscience of Addiction," <u>Neuron</u> , 21:467-476, (1998)
D37	Krishek et al, "Regulation of GABA $_A$ Receptor Function by Protein Kinase C Phosphorylation," <u>Neuron</u> , 12:1081-1095, (1994)
D38	Kushner et al, "Gamma-vinyl GABA attenuates cocaine-induced lowering of brain stimulation reward thresholds," <u>Psychopharmacology</u> , 133(4):383-388, (1997) (Abstract only)
D39	Lehel et al, "A Chemiluminescent Microtiter Plate Assay for Sensitive Detection of Protein Kinase Activity," <u>Analytical Biochemistry</u> , 244:340-346, (1997)
D40	Lin et al, "Protein Kinase C Enhances Recombinant Bovine $\alpha 1\beta 1\gamma 2\delta$ GABA $_A$ Receptor Whole-Cell Currents Expressed in L929 Fibroblasts," <u>Neuron</u> , 13:1421-1431, (1994)
D41	Lovinger et al, "Ethanol Inhibits NMDA-Activated Ion Current in Hippocampal Neurons," <u>Science</u> , 243:1721-1724, (1989)
D42	Macfarlane et al, "Activation of $\beta$ -Isozyme of Protein Kinase C (PKC $\beta$ ) Is Necessary and Sufficient for Phorbol Ester-induced Differentiation of HL-60 Promyelocytes," <u>The Journal of Biological Chemistry</u> , 269(6):4327-4331, (1994)
D43	Marszalec et al, "Selective Effects of Alcohols on $\gamma$ -Aminobutyric Acid A Receptor Subunits Expressed in Human Embryonic Kidney Cells," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 269(1):157-163, (1994)
D44	Mehta et al, "Ethanol Potentiation of GABAergic Transmission in Cultured Spinal Cord Neurons Involves $\gamma$ -Aminobutyric Acid $_A$ -Gated Chloride Channels," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 246(2):558-564, (1988)
D45	Meiner et al, "Disruption of the acyl-CoA:cholesterol acyltransferase gene in mice: Evidence suggesting multiple cholesterol esterification enzymes in mammals," <u>Proc. Natl. Acad. Sci. USA</u> , 93:14041-14046, (1996)

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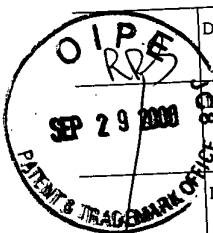
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| D46 | Mello et al, "A Primate Model of Polydrug Abuse: Cocaine and Heroin Combinations," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 274(3):1325-1337, (1995)  |
| D47 | Messing et al, "Chronic Ethanol Exposure Increases Levels of Protein Kinase C $\delta$ and $\epsilon$ and Protein Kinase C-mediated Phosphorylation in Cultured Neural Cells," <u>The Journal of Biological Chemistry</u> , 266(34):23428-23432, (1991) |
| D48 | Miyakawa et al, "Fyn-Kinase as a Determinant of Ethanol Sensitivity: Relation to NMDA-Receptor Function," <u>Science</u> , 278:698-701, (1997)  |
| D49 | Nestler et al, "Molecular and Cellular Basis of Addiction," <u>Science</u> , 278(5335):58-63, (1997)  |
| D50 | Nishizuka, "Intracellular Signaling by Hydrolysis of Phospholipids and Activation of Protein Kinase C," <u>Science</u> , 258(5082):607-614, (1992)  |
| D51 | Ohmichi et al, "Nerve growth factor activates calcium-insensitive protein kinase C- $\epsilon$ in PC-12 rat pheochromocytoma cells," <u>Biochem. J.</u> , 295:767-772, (1993)   |
| D52 | Olive et al, "Differential behavioral and neurochemical responses to ethanol in mice lacking protein kinase C - epsilon," <u>Alcoholism Clinical and Experimental Research</u> , 23:21a, (1999)   |
| D53 | Ono et al, "The Structure, Expression, and Properties of Additional Members of the Protein Kinase C Family," <u>The Journal of Biological Chemistry</u> , 263:6927-6932, (1988)   |
| D54 | Pahlman et al, "Kinetics and concentration effects of TPA-induced differentiation of cultured human neuroblastoma cells," <u>Cell Differentiation</u> , 12:165-170, (1983)  |
| D55 | Papadopoulos et al, "Isolation and Characterization of Protein Kinase C from Y-1 Adrenal Cell Cytoskeleton," <u>The Journal of Cell Biology</u> , 108:553-567, (1989)   |
| D56 | Pennisi, "Enzyme Linked to Alcohol Sensitivity in Mice," <u>Science</u> , 278:573, (1997)   |
| D57 | Poisbeau et al, "Modulation of Synaptic GABA <sub>A</sub> Receptor Function by PKA and PKC in Adult Hippocampal Neurons," <u>The Journal of Neuroscience</u> , 19(2):674-683, (1999)  |
| D58 | Powell et al, "Protein kinase C isozymes $\epsilon$ and $\alpha$ in murine erythroleukemia cells," <u>Proc. Natl. Acad. Sci. USA</u> , 89:147-151, (1992)   |
| D59 | Reich et al, "Genome-Wide Search for Genes Affecting the Risk for Alcohol Dependence," <u>American Journal of Medical Genetics (Neuropsychiatric Genetics)</u> , 81:207-215, (1998)   |
| D60 | Roivainen et al, "Protein kinase C and adaptation to ethanol," in <u>Toward a Molecular Basis of Alcohol Use and Abuse</u> , 29-37, (Jansson et al., eds., Birkhauser Verlag, 1994)   |
| D61 | Roivainen et al, "Ethanol enhances growth factor activation of mitogen-activated protein kinases by a protein kinase C-dependent mechanism," <u>Proc. Natl. Acad. Sci. USA</u> , 92:1891-1895, (1995)   |
| D62 | Roivainen et al, "Protein kinase C isozymes that mediate enhancement of neurite outgrowth by ethanol and phorbol esters in PC12 cells," <u>Brain Research</u> , 624:85-93, (1993)   |
| D63 | Roth et al, "Rat Brain Protein Kinase C: Purification, Antibody Production, and Quantification in Discrete Regions of Hippocampus," <u>Journal of Neurochemistry</u> , 52:215-221, (1989)   |

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D64	✓	Sanchez-Perez et al, "Increased acute responses to ethanol and enhanced sensitivity of GABA-A receptors to ethanol and benzodiazepines in PKC epsilon mutant mice," <u>Alcoholism Clinical and Experimental Research</u> , 23:12a, (1999)
D65	✓	Sapp et al, "Ethanol-GABA <sub>A</sub> Receptor Interactions: A Comparison between Cell Lines and Cerebellar Purkinje Cells," <u>The Journal of Pharmacology and Experimental Therapeutics</u> , 284(2):768-776, (1998)
D66	✓	Schuckit, "Low Level of Response to Alcohol as a Predictor of Future Alcoholism," <u>Am. J. Psychiatry</u> , 151:184-189, (1994)
D67	✓	Selbie et al, "Molecular Cloning and Characterization of PKC <sub>γ</sub> , an Atypical Isoform of Protein Kinase C Derived from Insulin-secreting Cells," <u>The Journal of Biological Chemistry</u> , 268(32):24296-24302, (1993)
D68	✓	Sharpe, "Researchers Say Hoechst Drug May Be Treatment for Cocaine, Nicotine Addicts," <u>Wall Street Journal</u> , Aug. 5, 1998
D69	✓	Sigel et al, "Recombinant GABA <sub>A</sub> receptor function and ethanol," <u>FEBS Letters</u> , 324(2):140-142, (1993)
D70	✓	Slawecki et al, "Differential Changes in Sucrose/Ethanol and Sucrose Maintained Responding by Independently Altering Ethanol or Sucrose Concentration," <u>Alcoholism: Clinical and Experimental Research</u> , 21(2):250-260, (1997)
D71	✓	Stewart et al, "Expression of retroviral vectors in transgenic mice obtained by embryo infection," <u>The EMBO Journal</u> , 6(2):383-388, (1987)
D72	✓	Suen et al, "NMDA receptor subunits in the postsynaptic density of rat brain: expression and phosphorylation by endogenous protein kinases," <u>Molecular Brain Research</u> , 59:215-228, (1998)
D73	✓	Uchida et al, "Affinity Chromatography of Protein Kinase C-Phorbol Ester Receptor on Polyacrylamide-immobilized Phosphatidylserine," <u>The Journal of Biological Chemistry</u> , 259(20):12311-12314, (1984)
D74	✓	Valverde et al, "Molecular cloning and characterization of protein kinase D: A target for diacylglycerol and phorbol esters with a distinctive catalytic domain," <u>Proc. Natl. Acad. Sci. USA</u> , 91:8572-8576, (1994)
D75	✓	von Melcher et al, "Selective disruption of genes expressed in totipotent embryonal stem cells," <u>Genes and Development</u> , 6:919-927, (1992)
D76	✓	Wafford et al, "Genetic Differences in the Ethanol Sensitivity of GABA <sub>A</sub> Receptors Expressed in <i>Xenopus</i> Oocytes," <u>Science</u> , 249:291-293, (1990)
D77	✓	Wafford et al, "Ethanol Sensitivity of the GABA <sub>A</sub> Receptor Expressed in <i>Xenopus</i> Oocytes Requires 8 Amino Acids Contained in the γ2L Subunit," <u>Neuron</u> , 7:27-33, (1991)
D78	✓	Walton et al, "A Three-Step Purification Procedure for Protein Kinase C: Characterization of the Purified Enzyme," <u>Analytical Biochemistry</u> , 161:425-437, (1987)
D79	✓	Weiner et al, "Elevation of Basal Protein Kinase C Activity Increases Ethanol Sensitivity of GABA <sub>A</sub> Receptors in Rat Hippocampal CA1 Pyramidal Neurons," <u>Journal of Neurochemistry</u> , 68:1949-1959 (1997)

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